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Severe Diphtheria: Diphtheria is caused by the growth of virulent Corynebacterium diphtheriae in a susceptible host. The primary infection in the majority of cases occurs in the respiratory tract, though lesions in the skin are not uncommon and other sites are occasionally involved. This bacterial infection tends to be a localized one, and though the whole respiratory tract may often be involved from the nares to the bronchioles, invasion of the deeper tissues by the organisms with suppuration or spread into the lymphatics or blood stream almost never occurs. The soluble toxin elaborated from C. diphtheriae is readily absorbed and is capable of producing serious damage to some of the body's most vital cells; those of the myocardium, nervous system, and the adrenals are particularly susceptible.

Despite immunization programs, diphtheria still presents a problem of great importance to the general medical profession for the following reasons:

1. There has been an increase in prevalence of diphtheria throughout the United States in the past few years.
2. There seems to be a tendency toward a rising average age of incidence.
3. Neither a history of immunization nor a history of a previous attack can be considered to rule out a diagnosis of diphtheria.
4. Most patients with diphtheria can be cured if the disease is recognized early and if treatment with adequate amounts of antitoxin is instituted immediately.

The object of the present study was to point out the clinical and pathologic features of the more severe forms of diphtheria by an analysis of a group of 30 cases which have recently come under observation. Five of the patients were treated at The Johns Hopkins Hospital and 25 at The Sydenham Hospital for Infectious Diseases. Except for 3 of those at The Johns Hopkins Hospital they were seen from 1945 through 1947.

Aside from a story of exposure to a known or suspected case of diphtheria, there is little of real diagnostic importance in the patients' history or symptoms that will differentiate this from other acute infections of the upper respiratory tract. The initial symptoms are usually sore throat and rather marked prostration, but the temperature is only moderately elevated. Vomiting, particularly in children, is of common occurrence, but probably not more so than in other acute infections. Following this there are frequently symptoms of partial obstruction of the nares, pharynx, or larynx, depending on the location of the infection. A sanguineous discharge from the nose, though its incidence is not high, is suggestive of diphtheria. The diagnosis is seldom suspected during the first 2 or 3 days, and the patients are usually given symptomatic treatment or one of the sulfonamides. Twelve patients out of the 30 in this series gave a history of immunization with toxoid. This problem deserves further analysis and study in order to determine whether or not enough doses of toxoid had been given, whether the standard toxoid is maximally antigenic, etc.

In these 30 patients the duration of the symptoms prior to diagnosis and treatment varied from 2 to 17 days, with an average of 4.7 days. The chief reason for the failure to make an early diagnosis in diphtheria is not so much the lack of specificity of the symptoms and signs as it is the failure of the physician to consider this as a prominent possibility in all patients with acute infections of the upper respiratory tract.

The patient with diphtheria is apt to appear more ill and prostrated than might be expected from the elevation of temperature, and there is often tachycardia which is out of proportion to the fever, in comparison with other acute respiratory infections. A bloody nasal discharge is an important finding from a diagnostic standpoint - as mentioned earlier. The localized area of involvement - whether it be in the nose, throat, or larynx - usually presents a tough, membranous type of exudate attached firmly to the tissues and tending to be confluent rather than spotty or punctate. The borders of the "membrane" are usually fairly sharply demarcated and the surrounding tissues, particularly those in the pharynx, show varying degrees of edema and redness. This edema at times tends to be so marked that it is nearly impossible to get a good view of the posterior pharyngeal wall, and the exudate itself may be entirely hidden. It is in this type of case that the diagnosis of diphtheria is frequently overlooked and precious time may be lost in waiting for the culture reports. The most typical local lesions are those in which there is a membrane in the nares or the larynx, or on the posterior pharyngeal wall and extending up over the soft palate and uvula. In such cases a positive diagnosis can be made at once and antitoxin given immediately.

Cervical adenitis of greater or lesser degree is present in nearly all patients, and in the tonsillar or pharyngeal types it often becomes marked. Frequently, in the patients who are severely ill the adenitis is accompanied by a marked edema that is brawny in character, tender to touch, and that obliterates the normal curves between the mandible and the clavicle. This results in the so-called "bull-neck" appearance. This condition has been encountered so frequently during the recent epidemics, and has been associated so regularly with the most severe types of infection, that the term "bull-neck" diphtheria is often used to describe a particularly malignant variety. In the present series the bull-neck swelling was a prominent feature in 18 cases (60 percent).

Laryngeal or tracheobronchial obstruction was encountered in 15 (50 percent) of the patients and was nearly always relieved by prompt tracheotomy and suction. The suction could usually be accomplished successfully by rubber catheters, but repeated bronchoscopic aspiration was often necessary. These patients showed varying degrees of obstruction, with wheezing difficult respirations, cyanosis, and retraction of the interspaces or of the whole chest wall with inspiration. Signs of atelectasis or pneumonia also may be present. After tracheotomy, pieces of membrane may be aspirated, and at times whole casts of the trachea or of the tracheobronchial tree can be obtained. Such procedures result in dramatic improvement in the patient's condition, but may need to be repeated many times.

Most patients who suffer from the severe form of diphtheria show evidence of myocardial involvement; it causes death in a high proportion of them. Evidence of myocardial damage was shown in 27 cases of this group. This is usually determined, particularly in the sickest patients, on clinical grounds, but in others only electrocardiographically. The myocardial damage may occur during any stage of the infection; in some it occurs early and as part of an overwhelming toxemia; in most it is found during the height of the disease; and in others it appears late, and the symptoms may develop suddenly when the patient seems well on the way to recovery. Many times it is accompanied by sudden circulatory collapse; this, however, is not always associated with demonstrable myocardial changes pathologically. The most reliable clinical signs of diphtheritic myocarditis are: a soft or weak first heart sound, particularly if a definite change has been noted in this sound from previous observation; an increase in heart rate; a fall in blood pressure; and in some cases enlargement of the liver. This latter finding is most commonly noted in young children. Arrhythmias of various types may be noted. Extrasystoles and complete heart block are apparent from clinical grounds, and tachycardias such as ventricular tachycardia and auricular flutter usually are diagnosed electrocardiographically. Signs of congestive failure may occur in a few patients, if the patients survive long enough, but this is not a common finding. During the acute phase of the myocarditis in the patients studied recently at The Sydenham Hospital there was frequently found an increase in circulation time and sometimes a moderate increase in venous pressure. One of the authors has observed enough patients with these findings to feel that they offer methods by which the diagnosis of myocardial weakness may be determined early and a means of following the efficacy of treatment.

The electrocardiographic changes are varied and not specific for diphtheria, but alterations from the normal tracing are observed so commonly, even in the milder cases, that the electrocardiogram is useful in the diagnosis and prognosis of this complication. In this series the changes varied from the milder type, in which there was a slight alteration in the T-waves or increase in conduction time, to the most severe types such as complete heart block. The most significant findings in this group, with most patients showing more than one abnormality, were lowering or inversion of T-waves in 14 instances, depression of the S-T segments in 11, incomplete heart-block (including slight prolongation of the P-R interval) in 5, right axis deviation 5 times, and lowered voltage 5 times. Complete auriculo-ventricular block occurred 12 times and intraventricular block 9 times. Both of these were, of course, interpreted as evidence of advanced myocardial damage and as very grave prognostic signs, in most cases being found shortly before death. Ventricular tachycardia was diagnosed three times, auricular flutter twice, and auricular fibrillation once. The electrocardiograms were useful in determining the degree of myocardial damage and in following its trend.

Shock is a common occurrence in many types of acute infection, and particularly in diphtheria. Rich observed necrosis and "tubular degeneration" in the

fascicular layer of the adrenals in many patients dying of severe acute infections including diphtheria, and speculated on its probable importance in producing circulatory collapse. There were 5 instances in the present series in which this pathological finding was noted in patients in whom sudden circulatory failure developed just before death, and it was felt that it may have played an important role in the fatal outcome. In one of these there was no microscopic evidence of myocarditis. Attempts at replacement therapy with adrenal cortical substance so far have not proved effectual, though the dosage employed may not have been adequate.

Paralysis of various cranial or peripheral nerves is common in diphtheria; with cranial nerve paralysis occurring most often in the acute phase or slightly later, and peripheral nerve paralysis usually being delayed - sometimes as late as six weeks or more after the acute attack. The late type of nerve lesion, true nerve palsy, must be due to early fixation of the toxin in the nerve cells and then to very gradual changes in those cells, often taking weeks to develop to the clinical stage of peripheral neuritis. The recovery of the paralyzed muscles is slow, but usually complete. The earlier paralyses are due to muscular damage caused by local diffusion of the toxin. They are most apt to involve the palatal muscles, are more serious complications because they usually occur when the patient is most acutely ill and make the problems of feeding and respiratory exchange more difficult during this critical period.

Paralyses of one type or another were encountered in 9 patients in this series. In these cases there were 6 instances of palatal or pharyngeal paralysis; one each of ocular and diaphragmatic paralysis, and 4 instances of polyneuritis.

Although it is common to find a moderate degree of albuminuria at one time or another in severe cases of diphtheria, a diagnosis of nephritis does not seem justified unless there are repeated findings of heavy albuminuria, and often casts as well, in association with elevation of the nonprotein nitrogen in the blood. In 6 of the patients the diagnosis of nephritis was made on clinical grounds, but in none was it proved pathologically.

Cultures from the throat, nose, or trachea were positive in every case for C. diphtheriae, and in some instances the organism was grown from each of these sites. The routine virulence tests resulted in reports of "avirulent" organisms in 6 of the cases. In one patient the strain was found avirulent in one laboratory and virulent in the other, and in another the organism recovered from the trachea was found virulent and that from the nose avirulent. In none of these patients was there any question regarding the diagnosis of diphtheria. The methods employed in all these tests were the standard guinea-pig tests, which are done at times with the mixed culture, or more accurately with a pure culture. Ordinarily these are considered reliable tests for virulence, but it is obvious from this small series that they are not always accurate.

Various organisms other than C. diphtheriae were isolated in the routine cultures of the nose, throat, or trachea from most of the patients. In most cases a heavy growth was obtained, making it appear that they may have been of some clinical significance in increasing the severity of the infection. This seems more likely in the case of beta-hemolytic streptococci, than the others; this organism was recovered from 14 of the patients. It is because of the frequency of such cultural findings that the use of antibiotics or chemotherapy is justified.

Concerning differential diagnosis, if the pharyngeal lesion presents a confluent, membranous type of exudate, the diagnosis of diphtheria is very likely; whereas in the beta-hemolytic streptococcal type of acute tonsillitis or pharyngitis the exudate tends to be patchy and can be wiped off with a throat swab. The diphtheritic membrane is tough in consistency and is apt to leave a bleeding surface when scraped off. The patient with a streptococcal infection is apt to have a higher temperature than the one with diphtheria, and yet the latter usually appears more ill and is more apt to show signs of myocarditis. Smears and cultures should be taken from beneath the exudate and incubated immediately. When C. diphtheriae is present, a positive smear may be obtained from the culture medium in from 8 to 12 hours. In a case, however, in which there is any suspicion of diphtheria, antitoxin should be given. In Vincent's infections, the exudate is usually confluent and therefore hard to distinguish from that in diphtheria but the base has a tendency to ulcerate more deeply into the tissues. In these patients a smear taken from beneath the exudate will be positive for the fuso-spirochetal organisms characteristic of the infection. In a doubtful case a presumptive diagnosis of diphtheria should be made and the patient treated accordingly. Likewise, it is well to bear in mind that in an occasional case both infections may occur at the same time, and the diagnosis of diphtheria may be missed when that of Vincent's angina is established. In infectious mononucleosis, it is a fairly common occurrence for patients with the "anginal" type to be diagnosed as having diphtheria on the basis of the appearance of the throat. However, the correct diagnosis is usually made by the finding of enlargement of glands other than the local ones, a palpable spleen, and abnormal lymphocytes in the blood smear. The heterophile agglutinins appear in the blood in significant titers after from ten days to two weeks and help to settle the diagnosis. The authors have found several examples, however, of patients in whom both infections were present simultaneously. One of these patients, who was seen at The Johns Hopkins Hospital, showed all the characteristic features of infectious mononucleosis, and was treated as such for 10 days before the presence of diphtheria was determined. He continued to have fever and a membranous lesion in the throat from which positive cultures of C. diphtheriae were obtained only after the third attempt. The diphtheritic throat infection cleared up rapidly after antitoxin was administered. A child with a typical attack of croup may be no problem in diagnosis. However, there is a type of nondiphtheritic laryngitis, often associated with tracheitis and bronchitis, in which the child has a high fever, and may rapidly become seriously ill due to the acute infection and to respiratory obstruction. Such infections are usually caused by beta-hemolytic

streptococci, pneumococci, or Hemophilus influenzae and may be very hard to differentiate from diphtheria. The diagnosis may be made by examination of the throat and the larynx, and by cultures. However, it is often necessary to give diphtheria antitoxin when the diagnosis remains in doubt rather than wait for the cultures. Many times these patients with laryngo-tracheo-bronchitis require tracheotomy, which together with antibiotic or chemotherapy may be life-saving. In some cases of pharyngeal diphtheria the inflammatory edema is intense and localized enough to cause the tissues to bulge forward in the nature of a peritonsillar abscess. Consequently, many cases are so diagnosed and the suspected abscess is either incised or aspirated. This is a dangerous procedure in diphtheria, because the local situation is made worse rather than better. In any doubtful case, if it seems absolutely necessary to incise what seems to be a peritonsillar abscess, the patient should be given a large dose of diphtheria antitoxin first. In some patients with diphtheritic myocarditis the condition is confused at times with acute rheumatic fever, and in the absence of joint pains the differentiation may present some difficulties. This is particularly true of the cases in which the myocardial changes are not severe and in which there is no definite evidence of valve lesions. In such instances the diagnosis rests on careful examination of the local lesions and on repeated throat cultures

The early nerve lesions appearing during the height of the infection seldom present much of a diagnostic problem. However, the peripheral neuritis which usually has a delayed onset is often hard to differentiate from other types of neuritis. In these cases the primary infection may have been rather mild, and frequently the diagnosis of streptococcal pharyngitis had been made without taking cultures. In such patients the correct diagnosis is only suspected in retrospect, but may be supported occasionally by the persistence of positive throat cultures and residual changes in the electrocardiograms. The sequence of swallowing difficulty, loss of accommodation for near vision, then peripheral weakness - usually without paresthesias - is characteristic. In many cases the spinal fluid proteins are elevated, with no or only slight increase in cells. In this aspect, as well as in the character of the peripheral neuritis, diphtheritic polyneuritis may resemble the Guillian-Barre syndrome very closely.

The therapeutic problem in diphtheria involves three main categories: (a) neutralization of the circulating toxin as rapidly as possible, (b) relief of obstructive symptoms, and (c) maintenance of an efficient circulatory system. As soon as the diagnosis of diphtheria is suspected, the patient is tested for sensitivity to horse serum, and if the tests are negative, the antitoxin is given at once. If the tests are positive the antitoxin is given in small and increasing doses at intervals of approximately one-half hour until the total amount has been given; the usual precautions are observed concerning possible serum reactions. The usual method of administration is intramuscular for patients who are moderately ill, and intravenous for those whose infection is more severe. In most cases the total dose is given in one injection, and though there are no accurate methods of determining the exact amount needed, an excess of antibodies must be put into the blood as quickly as possible. In this group of

severely ill patients the dosage varied from a low of 40,000 units to a high of 220,000 units, with an average of 120,000. Except for one patient, who received 40,000 units, the minimum dose was 80,000, even in the case of small children. The average of 120,000 units in this series is quite high; this is the result of selection of the cases for their severity and the tendency to give larger doses to the more seriously ill patients. It is interesting to note, however, that in spite of this probable excess of antitoxin, the progress of the myocarditis in many of these patients was not obviously altered. In such cases the toxin presumably has been fixed by the cells of the myocardium early in the course of the infection. These tissues then may either go through a gradual or rapid process of cellular damage in spite of the antitoxin. It is important to be certain that there is an excess of antibodies in the blood as long as toxin is being formed at the site of the local lesion.

The wide experience at The Sydenham Hospital of Dr. Horace Hodes, Dr. Margaret Smith, and others has served to emphasize the importance of early tracheotomy, before cerebral anoxia has developed and before the child has become too fatigued from severe and prolonged respiratory effort. Aspiration, particularly in those whose obstruction is lower down and who develop atelectasis, by bronchoscope, often produces dramatic improvement. An oxygen tent is frequently necessary, and it is important that the atmosphere in the tent be saturated with water vapor and preferably kept at body temperature.

In treating derangements of the circulatory system in diphtheria, it has been found that digitalization is not only a safe therapeutic procedure when carried out carefully but one that may be of real benefit, even during the acute phase of myocarditis, and is not contraindicated by signs of severe damage to the conduction system. The treatment of this "shock," when fully developed, is difficult and on the whole has been unsatisfactory in the patients who are critically ill. Oxygen is given and a cautious attempt may be made to support the circulation with intravenous fluids, and thus to tide the patient over the most acute phase of the illness. Other substances, such as 50-percent glucose, ascorbic acid, and adrenal cortical hormone have been tried, but without evidence of any real benefit.

Penicillin was given intramuscularly in most of these patients during the past 2 years or more. In spite of the fact that C. diphtheriae is sensitive to penicillin, it was not found that the disease itself was altered by its use, the probable explanation being that there is no evidence of its having any effect on the toxin.

Autopsy data have been examined for 13 of 21 patients who died. In 8 of these there was dilatation of the heart which was usually described as marked. There was microscopic evidence of myocarditis in 9; this was often very extensive and involving all chambers of the heart, at other times it was of mild degree. In this respect the predominant changes varied from cellular infiltration

to necrosis of myocardial fibers and finally to extensive areas of fibrosis. In 2 cases no evidences of myocarditis could be found microscopically, though on clinical grounds the patients were thought to have definite evidence of myocardial damage. In one of these there were advanced electrocardiographic abnormalities to support this opinion, and yet at autopsy the only microscopic changes noted in the myocardium were widespread petechial hemorrhages. It is possible in such cases that the duration of the presumed myocarditis may have been too short to lead to changes which were visible microscopically; likewise, the petechiae may have played a role in production of the cardiac abnormalities. Lobular pneumonia was found in 4 cases, purulent bronchitis in 3, and some degree of atelectasis in 2. The local membranous lesion was observed in 7 instances and in the rest it had apparently disappeared and the local ulcerations healed. None of the patients showed a true "diphtheritic nephritis." The adrenals were involved in 7 cases, and in 5 of these the lesions were quite marked. These changes consisted of necroses and "tubular degeneration" in the fascicular layer of the cortex as had been described previously by Rich. The lesions in these patients were likewise either found or verified by Doctor Rich. They may be significant in helping to explain the occurrence of circulatory collapse and death. (Bull. Johns Hopkins Hosp., Oct. '48 - A. M. Fisher and S. Cobb)

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The Role of Allergy in the Pathogenesis of Purpura and Thrombocytopenia: Allergy by one term or another has been recognized as an etiologic factor in purpura since the earliest descriptions of that disease. Until very recently, however, the intangible nature of both allergy and purpura, the multiplicity of potential etiologic factors, and the lack of exact knowledge of the pathologic changes in purpura have made determination of the relative importance of allergy virtually impossible. Even now it is very difficult to evaluate the role of the allergic mechanism with accuracy.

For a number of years the author has used the term "purpura" to indicate vascular changes only. These vascular changes are characterized by reversible alterations of as yet unknown character in the walls of the smaller vascular radicles which make possible the escape of whole blood from the vascular bed. Such escape may occur more or less spontaneously (petechiae, nontraumatic ecchymoses) or it may be induced by increasing the intravascular pressure (e.g., "tourniquet test," Göthlin test, etc.) or by decreasing the extravascular pressure ("suction test," capillary resistometer, etc.). Artificial induction of petechiae is the most satisfactory criterion for the diagnosis of purpura at the present time, although lack of standardization of technics and variability of the vascular changes have made interpretation somewhat difficult. After comparative trial of the various tests, reliance has been placed almost entirely upon a simple "tourniquet test" done with a pneumatic arm band at 100 mm. of mercury (unless the systolic pressure is below that level, in

which case it is correspondingly reduced) and maintained for 8 minutes, unless extravasation of blood is marked, in which case it is stopped at a shorter time. A representative area 2.5 cm. in diameter is chosen, and the petechiae in it are either counted or recorded graphically. More than ten easily seen petechiae within the circle is regarded as a positive test, and the petechiae in excess of that number may be regarded as a quantitative expression of the test. A positive test is interpreted to indicate the presence of purpura, but a single negative test is not adequate to rule it out because of the variable nature of the vascular changes.

Purpura in this sense may and does most frequently exist alone. It may, however, coexist with or be complicated by defects in the coagulation or clot retraction mechanism of the blood (hypoprothrombinemia, thromboplastin deficiency, thrombocytopenia, fibrinogenopenia) in which cases the combination of inadequate blood coagulation and "leaky" vascular walls produces a hemostatic error of such magnitude as to cause serious blood loss. From a clinical standpoint, it is simpler to separate the vascular and hematologic factors and, at least for the purpose of etiologic studies, to consider thrombocytopenic purpura as purpura with thrombocytopenia or as two coexisting abnormalities. The importance of this dual approach is apparent in tracing the chronologic development of the knowledge of the etiology of these states.

Unfortunately, methods for the clinical study of the allergic mechanism in the production of thrombocytopenia, which has been so convincingly demonstrated experimentally, have been relatively unsatisfactory. However, thrombocytopenia with purpura following ingestion of various drugs has been reported by Loewy, Peshkin and Miller, and others, and thrombocytopenia has been produced at will in some of those patients by readministration of the offending drug and by skin testing, thus establishing the reaction as of allergic type in those patients. Further, demonstration of the allergic mechanism responsible for the granulocytopenia in certain cases of agranulocytic angina, and of the fact that sensitivity could be detected in those instances by the granulocytopenic response following ingestion of the offending allergens, has suggested that in certain cases the platelets might behave in a similar manner and has corroborated the soundness of the "ingestion" method of demonstrating thrombocytopenic response to allergenic substances. Utilizing that method of testing, in addition to the usual allergic diagnostic methods, it has been increasingly possible in recent years to establish allergic reactions as one of the causes of clinical thrombocytopenia with or without purpura. Squier and Madison and others have shown that allergenic foods are capable of producing thrombocytopenia in some persons; these investigators demonstrated platelet reduction following ingestion of such foods, and showed return of the platelet count to normal levels and clinical recovery after the removal of the offending foods from the diet.

Thus, allergy has been established as one of several factors capable of producing thrombocytopenia and likewise as one of several similar factors that are

capable of producing the vascular changes characteristic of purpura. The curious similarity of these etiologic factors may well explain why purpura occurs so much more frequently in association with thrombocytopenia than with hypoprothrombinemia or thromboplastin deficiency. In the case of the allergic factor it is readily conceivable that an allergic individual might have both hematologic and vascular response simultaneously and to the same allergen, producing typical "thrombocytopenic purpura." Clinical evidence to support this possibility is accumulating slowly, and is derived principally from satisfactory clinical response of both thrombocytopenia and purpura to allergic control without splenectomy. With advances in the technic of studying allergic states, and with wider use of the ingestion method of testing, it is likely that more cases will be found to fall into the allergic category and to respond favorably to that method of therapeutic approach. (Blood, J. Hematol., Oct. '48 - F. W. Madison)

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A Study of the Bone Marrow From Thirty-Six Patients with Idiopathic Hemorrhagic (Thrombocytopenic) Purpura: The majority of observations relating to the megakaryocytes and to the bone marrow in idiopathic thrombocytopenic purpura have been made on autopsy material, and there have been relatively few quantitative studies of material aspirated from the marrow in living patients. General statements are often made concerning the value of the bone marrow examination in thrombocytopenic conditions, but specific facts are few. Because of the paucity of quantitative information, a lack of correlation of the marrow findings with prognosis, and differences of opinion concerning the number and morphology of megakaryocytes, a further study of the bone marrow seems justified.

In this paper the observations made at the Cleveland Clinic on the bone marrow smears of 36 patients with idiopathic thrombocytopenic purpura, and the correlation of the findings with the clinical picture, are presented.

All of the patients had in common purpura, spontaneous bleeding from mucous surfaces, platelet counts below 100,000 per cu. mm., prolonged bleeding time, defective clot retraction, and normal or only slightly prolonged coagulation time. Smears from patients with demonstrable primary disease, leukemia, aplastic anemia, malignancy, nephritis, cirrhosis, or infections, or who gave a history of allergy or of taking drugs previous to hemorrhagic episodes, were excluded. Splenectomies, performed on 22 of the 36 patients, revealed normal or only slightly enlarged spleens. The tissue changes in the spleen were consistent with the diagnosis of thrombocytopenic purpura as defined by Nickerson and Sunderland. Almost all observations were made on marrow aspirated during the acute hemorrhagic phase of the disease.

The marrow was obtained by needle puncture of the body of the sternum in the midline at the level of the third rib. A minimal amount of marrow was aspirated, usually less than 0.2 c.c. Smears were made directly from the point

of the needle using the coverslip technic and stained with Wright's stain. Smears which contained relatively few nucleated red cells or early myeloid cells, and which were obviously diluted with peripheral blood, were not included in this study.

A control series consisted of 50 patients with nonhemorrhagic conditions without blood dyscrasias.

The principal value of the bone marrow examination in suspected cases of thrombocytopenic purpura is to differentiate it from aplastic anemia, leukemia, and other conditions. In making this differentiation the megakaryocyte plays a part, but the other cells play a major role.

The bone marrow in idiopathic thrombocytopenic purpura shows hyperplasia. It is cellular and there is little fat. There is a slight myeloid and erythroid immaturity, and in some cases a slight eosinophilia and lymphocytosis. The erythroid-myeloid ratio is normal in the majority of instances.

The megakaryocyte counts ranged from 3 to 59 per 10,000 nucleated cells, with an average of 17. In the control series the megakaryocytes ranged from 1 to 54 per 10,000 nucleated cells, with an average of 16.

There appears to be no correlation between the number of megakaryocytes found in the marrow smears during the acute phase of the disease and the prognosis with or without splenectomy. There is also no apparent correlation between the number of megakaryocytes and the platelet response following splenectomy.

The megakaryocytes were classified as megakaryoblasts, immature, intermediate, or mature megakaryocytes, or as naked nuclei. The principal criteria for the differentiation of megakaryocytes are the granules and the presence or absence of granular platelets.

The differential megakaryocyte counts were made by examining 25 or more megakaryocytes. In the control series the mature megakaryocytes which are actively producing platelets are the predominant cells, whereas in idiopathic thrombocytopenic purpura the intermediate cell without platelet production is predominant.

Marrow studies on 2 of the patients before and after splenectomy revealed a decrease in the relative number of megakaryocytes and an increase in the number of platelet-producing cells following operation.

No correlation was found between the eosinophil counts and the deaths, recurrences, or cures with or without splenectomy.

The variation in the number of megakaryocytes in different individuals with idiopathic thrombocytopenic purpura is in part due to true differences in individuals and in the distribution of these cells as has been shown in biopsy material by Lawrence and Knutti and in autopsy material by others, but much of the variation is due to dilution of the marrow cells with peripheral blood and to other technical factors. Megakaryocytes and particularly early forms are partially fixed cells which are not readily aspirated. These cells are fragile and easily destroyed by any manipulative procedure. They contain large amounts of thromboplastin and tend to get caught in fibrin webs which rapidly form around them. They are large cells which are pushed toward the margins and ends of slide preparations. The authors have found that in the best of coverslip preparations the megakaryocytes were unevenly distributed and that counts made on the same smears by the same or different individuals vary widely.

Because of unavoidable errors involved in megakaryocyte counting, a wide range of variation in different individuals, and no correlation between the megakaryocyte counts and prognosis within the range of observed values, it is obvious that there is little use in undertaking the laborious task of making actual counts.

Prognosis and indications for splenectomy are determined, not from the megakaryocyte study alone, but from the study of the entire patient. If the diagnosis is aplastic anemia, leukemia or secondary thrombocytopenia, splenectomy is not indicated.

If, in 2 drops of material aspirated from the marrow (4 coverslip or two slide preparations), there are twenty or more megakaryocytes, if the majority of them are immature or intermediate and not actively producing platelets, and if the rest of the marrow, peripheral blood and clinical picture fits, the diagnosis of idiopathic thrombocytopenic purpura is made and splenectomy may be recommended.

The finding of numerous megakaryocytes which are actively producing granular platelets is against the diagnosis of idiopathic thrombocytopenic purpura or is indicative of a spontaneous remission in a known case. Splenectomy in such cases is contraindicated.

The peculiar distribution of megakaryocyte types in some patients with idiopathic thrombocytopenic purpura in which there are few mature forms, yet an increased number of naked nuclei, suggests that the intermediate cells disintegrate without going through the platelet-producing stage. This constitutes additional evidence that the low platelet count found in this disease is due to defective formation of platelets rather than to excessive destruction outside of the bone marrow. (Blood, J. Hematol., Oct. '48 - L. W. Diggs and J. S. Hewlett)

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The Value and the Limitations of the Coagulation Time in the Study of the Hemorrhagic Diseases: The determination of the coagulation time of the blood is among the most empirical procedures routinely employed in the clinical laboratory, and is one most prone to be misinterpreted. In a critical evaluation of this test, one must consider (1) the mechanics of the procedure, and (2) the physiological aspects, which require a translation of an observation *in vitro* into a probable behavior *in vivo* that is coordinated with other factors bringing about hemostasis.

All the common procedures for determining the coagulation time are based on timing the interval between the removal of the blood from the patient and the formation of sufficient fibrin to meet an arbitrarily designed end point. The objective of every test is to measure the intrinsic coagulative power of the blood. Obviously, therefore, trustworthy results can be obtained only by performing the test under constant and rigidly controlled conditions and by excluding all outside agents that influence the coagulation reaction. Of the latter, tissue juice is by far the most important since it contains thromboplastin. It is, therefore, of utmost importance to exclude all traces from the specimen of blood used for determining the clotting time. Clearly, blood obtained by skin puncture (capillary blood) is utterly unsuitable because not only does it contain an appreciable amount of tissue fluid, but even more serious, the amount varies and cannot be controlled. Thus Christie demonstrated that there were variations in the clotting time of the different drops of blood collected from the same puncture, and Lee and White cite the example of a hemophilic blood which had a coagulation time of 50 minutes for venous blood and only 5 minutes for capillary blood. It must be emphasized that the coagulation time of capillary blood, irrespective of the method used, is worthless and unreliable for clinical purposes. Even in taking blood by venipuncture enough tissue thromboplastin may occasionally gain entrance to reduce significantly the coagulation time, as Jaques and his co-workers have recently demonstrated. It is not unusual to obtain a coagulation time of from 8 to 10 minutes in a hemophilic subject, whose true coagulation time is one hour, merely by causing slight trauma in drawing the blood.

There is a distinct need for a simple and uniform procedure. In the United States the Lee-White test is gradually replacing the other methods. This procedure is simple and yields as much and as accurate information as any test of coagulation so far devised, but unfortunately the test has not been rigidly standardized and at present there is no strict uniformity in the details of the procedure.

In order to devise a standard procedure, it was necessary to consider the more important factors that influence the coagulation of blood in a test tube. They are (1) temperature, (2) size of tube, and (3) the nature of the surface of the tube. After thorough study of these three factors, the following procedure was adopted and is recommended for determining the coagulation time:

Blood is drawn by venipuncture, preferably with a No. 22 needle, into a dry syringe. If the determination cannot be made immediately, a syringe coated with silicone (Dry Film) should be used, and the blood kept in the syringe until the operator is ready for the test. In drawing the blood the tourniquet should be applied just prior to the puncture. If blood is not obtained immediately and without trauma, another vein should be selected and a new puncture made. One cubic centimeter of blood is transferred into each of 2 scrupulously cleaned test tubes (Pyrex 100 x 13 mm.). Since the test tubes are apt to vary slightly in size, only tubes having an internal diameter of 11 mm. should be selected. The tubes are immediately placed in a water bath kept at 37° C. A vacuum bottle fitted with a cork having a hole in which the test tube can be inserted serves as a handy portable water bath. The tube is gently tilted every 30 seconds and the end point taken as the moment when on tilting no flow of blood is any longer observed. The normal range is from 5 to 10 minutes with the majority of bloods clotting between 6 and 8 minutes.

It should be emphasized that the end point selected is arbitrary and does not mark the time of complete coagulation. Unconverted fibrinogen may still be demonstrated. A convenient way to measure incipient coagulation is to insert a glass rod coated with collodion into 1 c.c. of blood and then withdraw it gently every 30 seconds. A fine thread of fibrin marks the beginning of coagulation. In normal blood, coagulation usually begins in from 3 and 1/2 to 4 minutes and is complete in 10 minutes, whereas in hemophilic blood coagulation may begin (to cite a specific observation) in 10 minutes but require 2 hours more before enough fibrin is formed for a solid clot. The tube with the glass rod should not be used for determining the final coagulation time.

From recent studies, evidence has been obtained to show that platelets do not furnish thromboplastin, but that in their disintegration they liberate an agent, probably an enzyme, that activates thromboplastin which occurs in the plasma as a precursor and for which the term, thromboplastinogen, has been proposed. It is probably identical with the antihemophilic globulin of Minot and Taylor and the prothrombokinin of Lenggenhager.

According to this new concept, the first step in coagulation can be expressed as follows:

(1) Thromboplastinogen $\xrightarrow{\text{platelet enzyme}}$ thromboplastin

The activated thromboplastin reacts immediately:

(2) Thromboplastin + prothrombin + calcium = thrombin

(3) Fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin

The first and third equations are enzymatic, whereas the second is stoechiometric. Thus, even a small number of platelets is sufficient to activate enough thromboplastin to furnish a quantity of thrombin that will coagulate blood within the normal period of time. Such a quantity of thrombin may, however, be entirely inadequate, as will be discussed later, to meet the hemostatic requirements. To understand the significance of the coagulation time, it should be remembered (1) that normal human blood could clot in 12 seconds if it had an otpimum amount of thromboplastin and (2) that furthermore, the curve correlating the coagulation time and the concentration of thromboplastin is a hyperbola with both asymptotes zero. This explains why the shortening of a coagulation time from 1 hour to 5 minutes can be brought about by an extremely small quantity of thromboplastin. The amount of thrombin formed depends on the quantity of prothrombin, thromboplastin, and calcium in the plasma, and this can be looked upon as the key to a better understanding of several important hemorrhagic diseases which will be considered in this presentation.

The coagulation time may be prolonged in four well known diseases or conditions: hemophilia, hypoprothrombinemia, afibrinogenemia, and heparinemia. It is possible that a delayed coagulation may occur in other conditions, but these have not been studied sufficiently to permit critical analysis. Hypercoagulability remains a vague and as yet meaningless term.

Hemophilia. With the exception of complete incoagulability of the blood as encountered in afibrinogenemia, the most prolonged coagulation times are observed in hemophilia. A coagulation time of one hour is not unusual, but a time of two hours or more is rather infrequent, provided the test is done carefully and at 37° C. It has been found in recent studies that the coagulation time of a hemophiliac may be surprisingly constant for a relatively long period of time. Thus, the coagulation time of one patient has remained about 55 minutes with few exceptions during the past 18 months. Although it has been brought to normal several times with plasma transfusion it has always promptly returned to this rather fixed value. The same constancy has also been found in other hemophiliacs, but in no instance has the period been long enough to be significant.

To understand the coagulation time in hemophilia, it is necessary to understand the basic defect in this disease. In a recent study it has been found that hemophilic blood is almost completely devoid of thromboplastinogen; and even after all the fibrinogen has coagulated, no demonstrable consumption of prothrombin has occurred. All the coagulation is due therefore to a minute quantity of thrombin which is formed and which, because it is an enzyme, can convert all of the fibrinogen to fibrin in a relatively short time. The minuteness of the quantity of thromboplastin which can bring about a normal coagulation time is clearly demonstrated by the following experiment:

A stock extract of thromboplastin prepared by mixing 0.2 Gm. of dehydrated rabbit brain in 5 c.c. saline, was diluted from 1 to 1000. On adding 0.1 c.c. of

this diluted thromboplastin to 1 c.c. of hemophilic blood which had a coagulation time of 2 hours and 15 minutes, the time was reduced to 5 minutes. This 0.1 c.c. of thromboplastin contained only 2.5 gammas of solid material, of which a large fraction was inert. Obviously, the amount of thrombin formed must have been extremely small, yet it coagulated the blood in 5 minutes. The conversion of prothrombin, however, was so small that it could not be demonstrated.

From the results observed in hemophilia and in hypoprothrombinemia, it seems definite that hemostasis is not dependent on the clotting time but on the quantity of thrombin supplied during the clotting process. In hemophilia little thrombin is formed since the plasma lacks the thromboplastin precursor. Even if the plasma contains enough thromboplastinogen to cause a normal coagulation time, it may not be sufficient to supply enough thrombin for the hemostatic needs. This explains why a normal coagulation time may be found in known hemophiliacs suffering from repeated hemorrhages. In a limited number of such patients, the senior author could demonstrate no consumption of prothrombin after coagulation had been completed. Such patients are a problem to the surgeons since the normal coagulation may create a false sense of security. Furthermore, not every measure which reduces the coagulation time of a hemophiliac is necessarily effective in controlling hemorrhage. Just as the effectiveness of vitamin K cannot be established by the coagulation time but only by the decrease in the prothrombin time, so the assay of any antihemophilic agent cannot be made with an absolute degree of certainty by the coagulation time, but will probably require the measurement of the prothrombin consumption.

The coagulation time is obviously of limited value in hemophilia, either in the diagnosis or in the treatment. A prolonged value is suggestive of hemophilia provided other causes are ruled out. A normal coagulation time does not exclude a diagnosis of hemophilia. A history of bleeding together with a markedly poor consumption of prothrombin during coagulation appears to be much more reliable evidence on which to base a diagnosis.

The coagulation time, is, however, of some practical and theoretical value. A hemophiliac with a coagulation time that is nearly normal usually has mild attacks of bleeding and only encounters serious trouble when relatively large vessels are damaged. The severity of the bleeding tendency appears to be relatively independent of the coagulation time when the value of the latter exceeds from 15 to 20 minutes. In three hemophiliacs having average coagulation times of 25, 55, and 120 minutes respectively, the frequency and severity of the bleeding episodes during a period of observation of 6 months, were roughly the same. Theoretically, the coagulation time is of value since it offers the only means to grade the severity of the hemophilic defect. Thus, the difference in availability of thromboplastin between the three hemophiliacs mentioned is so small that no other test, including the prothrombin consumption, can detect the difference.

The coagulation time has, it should be mentioned, served not only in establishing the presence in plasma of an antihemophilic agent, but has enabled Minot,

Taylor and their associates to concentrate it. They wisely depended not so much on a transient lowering of the coagulation time but on a sustained normal value.

Hypoprothrombinemia. Prior to the advent of vitamin K, it was very puzzling to the surgeon why the jaundiced patient bled postoperatively in spite of a normal coagulation time. The senior author, on the basis of his early studies on vitamin K, concluded that the hemorrhagic danger level was indicated by a prothrombin time of about 25 seconds, which corresponds in man to a prothrombin activity of 20 percent of normal. At this level the coagulation time is so little increased that unless the test is done with great care it escapes detection, since it is still well within the normal range. In fact, it has been found that in dogs an increase of the prothrombin time from the normal of 6 seconds to 60 seconds is accompanied by a change of the coagulation time only from 3 and 1/2 to 5 and 1/2 minutes; i.e., an average increase of only 2 minutes. Even with extremely low concentrations of prothrombin, the coagulation time is rarely as prolonged as in moderately severe hemophilia. At very low levels, the prothrombin time and the coagulation time tend to become identical. Thus, on reducing the prothrombin in a dog with dicumarol until the prothrombin time was 20 minutes, a coagulation time of 19 minutes and a clotting time for recalcified plasma of 30 minutes was obtained. The likely reason for such a result is that the limiting factor is prothrombin and that under such circumstances the thromboplastin of the plasma is adequate, and therefore additional amounts of the latter have no further effect.

Early in the work on poisoning from toxic sweet clover, one of the authors discovered that a heart puncture in a rabbit with a reduced prothrombin caused fatal hematopericardium. Therefore, in this same way a study was carried out in rabbits, and a correlation was made between the prothrombin time, coagulation time, and the hemostatic breakdown. A study of the results clearly showed that when the prothrombin time is less than 19 seconds, cardiac bleeding does not occur. With a prothrombin time of 24 seconds or more, hematopericardium invariably occurred. Although there was a slight increase in coagulation time, no clear cut relation between it and fatal hemorrhage could be found. Interestingly, one of the authors observed a series of patients with congenital hypoprothrombinemia and has found that those with a prothrombin time of 16 seconds showed no hemorrhagic tendency, two patients with a prothrombin time of 19 seconds showed a distinct bleeding tendency, and one with a value of 30 seconds showed a very severe hemorrhagic condition.

Obviously the coagulation time is of little or no value in the study of hypoprothrombinemia. It cannot be used for controlling dicumarol therapy. Again, basically, the fact is brought out that hemostasis depends on the amount of thrombin formed, and when the prothrombin is reduced to about 20 percent, insufficient thrombin is furnished for checking the flow of blood.

Afibrinogenemia. When total incoagulability of the blood is found, afibrinogenemia should be suspected and a qualitative test for fibrinogen made. Recently, Pinniger and Prunty demonstrated experimentally that the prothrombin time remained approximately normal in the blood of their patient until the fibrinogen fell below 50 mg. per 100 c.c. of plasma, and that the Lee-White coagulation was 5 minutes when the fibrinogen concentration was as low as 30 mg. It is obvious that the coagulation time has little practical value in this hemorrhagic condition except in the initial detection of a coagulation defect.

Heparinemia. Animals, particularly dogs subjected to peptone or anaphylactic shock, respond by an outpouring of histamine and heparin into the blood, and by a marked thrombocytopenia. The resulting heparinemia may be so great that the blood is rendered incoagulable. In man, the appearance of heparin in the blood has not been unequivocally demonstrated although there is a good probability that it can occur. The increase of the coagulation time is not necessarily proportional to the concentration of heparin. The latter can be much more accurately determined by titration with progressive dilutions of a standard thrombin solution.

The therapeutic use of heparin in the prophylaxis of thrombosis is successfully controlled by the coagulation time, but this is entirely on an empirical basis because it has not been accurately determined how much heparin is needed for this purpose. It is probable that the effective action of heparin consists in neutralizing thrombin, and thus reduces the effective quantity of the latter.

From the foregoing discussion, it becomes clear that the coagulation time has limited value in the study of the known hemorrhagic diseases. It has, however, an important function in the possible discovery of new hemorrhagic diseases. On finding a prolonged coagulation, a concise diagnosis can be made only by specific tests such as the prothrombin time, and the prothrombin consumption test. A little over a decade or two ago, nearly all hemorrhagic diseases characterized by a coagulation defect were called hemophilia. Since then hypoprothrombinemia, afibrinogenemia, and heparinemia have been recognized as separate entities. It is highly probable that other hemorrhagic conditions having a prolonged coagulation time exist but thus far have not been recognized and defined because of a lack of suitable methods of study. (Blood, J. Hematol., Oct. '48 - A. J. Quick et al.)

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Further Experience with Thromboangiitis Obliterans in Women: Although thromboangiitis obliterans in women is still a rare disease, recent experience appears to show that it is occurring with increasing frequency. In the first 1,000 patients with this disease seen by the writer, there were only two women, but in the last 600 there have been 23 women. Although the incidence for the entire group is only slightly over 1 percent, in the past ten years it has risen to 4 percent.

During the past 25 years women in increasing numbers have adopted the habit of smoking, and many of them smoke excessively. Because, in the author's opinion, the use of tobacco by individuals susceptible to this substance is the etiological factor causing thromboangiitis obliterans, it is not difficult to understand why more women are showing signs of this illness. Furthermore, this trend is likely to become more pronounced in the future. Physicians must be alert to the possibility that circulatory disease of this type may be present in young female patients who complain of discomfort in the extremities.

This presentation is based upon the study of 25 female patients with thromboangiitis obliterans seen in private and clinic practice. The essential criterion used in making this diagnosis was the presence of symptoms and signs of obliterative vascular disease in the extremities in women between the ages of 20 and 45 years. A history of intermittent claudication, coldness of the extremities or change of color with different positions of the extremities was usually present in varying degree. The occurrence of superficial phlebitis or painful ulcerations of the fingers or toes with operative or spontaneous loss of digits or amputation of the extremities in persons in this age group gave added weight to the diagnosis of thromboangiitis obliterans. Absence of some major pulsations in the upper or lower extremities was noted in nearly all cases. Evidence of impairment in the circulation was confirmed by oscillometric studies in all cases and by temperature studies in some.

In order to exclude individuals with peripheral vascular disease due to arteriosclerosis, patients with diabetes, gout, or syphilis were not considered in this series. These disorders are known to hasten the development of arteriosclerosis. Hypertension militated against the inclusion of a case when it was clear that an elevated blood pressure had existed prior to the appearance of symptoms of arterial obstruction. Individuals in whom calcified vessels could be visualized by x-ray films were excluded. Arteriosclerotic vascular disease without roentgenographic evidence of calcification is frequently present in patients who first present symptoms of impaired circulation between the ages of 45 and 55 years, and such cases were not included in this series.

There follow two out of the 25 case histories presented by the author:

Case 15. T.P., a Hebrew woman, was 24 years of age when first seen at The Mount Sinai Hospital in March, 1944. For one and one-half years she had had pain in the left calf after walking five blocks or after dancing. She had been smoking 20 cigarettes a day. She was married but had no children. Examination showed a well-nourished young woman whose general physical examination was negative. The right radial and left ulnar pulses were absent. The right ulnar and left radial pulses were present. Both femoral pulses were present. The right popliteal and right posterior tibial pulses were present. The right anterior tibial and dorsalis pedis pulses were absent. The left popliteal artery was closed and there was no pulse in the left foot. The oscillometer

readings were: left calf, 0.5; left ankle, 0.25; right calf, 4; right ankle, 1.5. Blood pressure was 120/70. Blood Wassermann test was negative. It was difficult to persuade this patient to stop smoking, but she finally gave up using tobacco and was treated with intravenous injections of hypertonic salt solution. She showed steady improvement. In June, 1947, she was able to walk indefinitely without pain and without stopping. The pulses in her feet and the oscillometer readings remained unchanged. This young woman, like one other in this series, had thromboangiitis obliterans involving all her extremities.

Case 17. I.Y., an American Hebrew woman, was 29 years of age when first examined in 1945. Eight years previously she had had a superficial phlebitis of the left leg, and intermittent claudication had developed shortly afterward. In 1942, she had developed gangrene on the inner side of the right great toe. In 1943, she had had a right hemiplegia with aphasia. Ever since then she has had occasional short epileptic attacks involving the right side and characterized by clonic contractions lasting a few seconds; she has also had crying spells. She had begun to smoke when very young and smoked twenty cigarettes a day. She had stopped smoking in 1943. She was married but had no children. Examination showed a well-nourished young woman. There was weakness of the right side of the face and a hemiparesis of the right side of the body. She had almost complete motor aphasia but could speak a few words. There appeared to be no sensory aphasia. Her blood pressure was 130/80. Both radial arteries were open, but the ulnar arteries were closed. Both femoral arteries were open. Both popliteal arteries were closed. There was no pulse in either foot. There was a scar on the inner side of the right great toe. The oscillometer readings were: left calf, 1; left ankle, faint; right calf, 0.25; right ankle, 0. When she was last examined in June, 1947, her condition was unchanged. This young woman with typical thromboangiitis obliterans of all four extremities presented the extremely unusual complication of a right hemiplegia and motor aphasia, which had developed at the age of 27 years. Two other women in this series showed cerebral involvement.

Study of the case histories reveals certain facts which require emphasis. The most important finding is that thromboangiitis obliterans in women very frequently involves the hands, and occasionally begins in the fingers rather than in the feet. In men it is extremely rare for this disease to begin in the upper extremities. Fourteen of the 25 women (56 percent) showed signs of circulatory disease in the upper extremities.

When circulatory disease occurs in the hands of a woman, the differential diagnosis between thromboangiitis obliterans and Raynaud's disease becomes very important. Unless the proper diagnosis is made, treatment is almost certain to be incorrect and unsuccessful. Raynaud's disease is pre-eminently a condition which occurs in women, and involvement of the hands is characteristic. Patients with Raynaud's disease complain of blanching of the fingers on exposure to cold. This is due to spasm of the digital arteries shutting off

circulation to the finger tips. Female patients with thromboangiitis obliterans also complain of blanching of the fingers on exposure to cold. This is due to vasoconstriction superimposed upon organic disease in the digital vessels. The blanching in Raynaud's disease is likely to involve several fingers, and symmetrical fingers of both hands. The blanching in thromboangiitis obliterans is more likely to involve only one finger of one hand. Pain is not a prominent feature of Raynaud's disease. Patients with this condition complain of tingling during the hyperemic or red phase of the attacks, but between attacks there is usually no pain unless ulceration is present. In contrast, the patient with thromboangiitis obliterans complains of constant pain in the affected finger. This is an important clue to the nature of the illness. On examination, the patient with Raynaud's disease will show equal temperature of all fingers between attacks because it is only during the period of spasm that circulation is temporarily impaired. On the contrary, the patient with thromboangiitis obliterans will show persistent coldness of the involved finger at all times. Finally, examination of the lower extremities will reveal normal arterial circulation in Raynaud's disease, but some pulsations are likely to be absent in patients with thromboangiitis obliterans. If these points are kept in mind, it is usually possible to distinguish between the two conditions.

Of these 25 patients, 12 percent (3 patients) showed cerebral involvement as compared to less than 1 percent in male patients. However, because of the relatively small number of female patients with this disease, this figure cannot be considered significant unless it is confirmed in a much larger series of cases.

It is discouraging to note that women are even more prone to resume smoking and cause recurrence of their trouble than are men. Emotional disturbances, the tendency to put on weight, or recurrence of habit are given as the usual reasons. In such instances, when the patient returns, it is usually found that the circulation is much worse than when she was first seen, and the long course of treatment necessary to improve it must be resumed.

The opportunity to study many additional cases of thromboangiitis obliterans in women has thrown no further light upon the relative immunity of this sex to the disease. The women in whom thromboangiitis obliterans developed showed no changes in menstruation, child bearing, or physical characteristics to distinguish them from other members of the female sex. Dr. Robert T. Frank was kind enough to study the excretion of estrogens in all the urine passed for one month in two patients in this series. He was unable to detect any abnormalities in this respect. A family history of thromboangiitis obliterans was searched for, but was not found in any of the 25 women in this series. Unless future experience shows a much greater incidence of the disease in women, it may be necessary to accept as an explanation that women do not frequently inherit the tendency to develop specific sensitivity to tobacco which is apparently needed to make possible the development of thromboangiitis obliterans.

All of the women in this series with thromboangiitis obliterans were habitual smokers. Progression of the disease was regularly associated with the continued or resumed use of tobacco. All patients restored to good health who have refrained from smoking have remained in excellent condition.

The 25 case histories presented by the author show that 22 patients were Hebrew and 3 were non-Hebrew. (Am. Heart J., Nov. '48 - S. Silbert)

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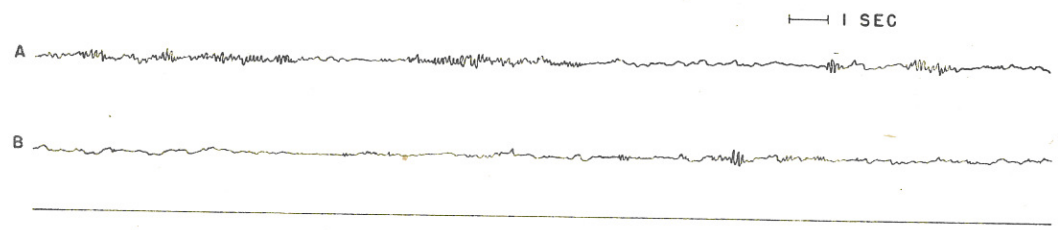
A New Electroencephalogram Associated with Thinking: In the course of experimentation on counting eye movements in reading by means of the corneo-retinal potential, with bipolar electrodes placed just back of the external canthi of the eyes, a 10-cycle per second disturbance in the reading record was noted. Further investigation indicated that this disturbance was, in actuality, a new electroencephalogram which the authors have designated "kappa waves." These kappa waves characteristically occur in intermittent spindle-shaped bursts. They have an average frequency of from 8 to 12 cycles per second and an average amplitude of around 20 microvolts.

Several situations have been found which dependably produce kappa waves. One of these is mental arithmetic. The figure below is a composite tracing of two equivalent sections of record. Line A is the electroencephalogram taken



from the canthal placement on a subject engaged in multiplying two-digit numbers (eyes fixated). Line B is a comparable record when the subject was attempting to "keep his mind a blank" (eyes fixated). The greater amount of kappa rhythm in mental multiplication is evident. Kappa intrudes occasionally when the subject is trying not to think. Introspective reports suggest that the intrusions of kappa correspond to "thoughts" during the period of attempted voluntary inhibition of thinking. Difficult discriminations evoke kappa bursts. Other situations which have been found to bring out a large amount of this rhythm are (1) learning tasks, such as nonsense syllables; (2) memory tasks, such as naming the 48 states; and (3) problem solving, such as that involved in mastering a finger maze. In general, kappa waves have been found to be most prevalent in situations which are usually classed as involving thinking.

Out of 31 subjects tested with bipolar electrodes placed just back of the external canthi of the eyes, 18 showed a recognizable amount of activity of

from 8 to 12 cycles per second. Attempts were made to record these waves on subjects not initially exhibiting them by using other electrode placements on the front part of the head. For the most part, these attempts were unsuccessful. Further investigation is required to determine whether kappa waves are actually absent in subjects showing little or no from 8- to 12-cycle bursts from the canthal placement. The possibility of such factors as poor condition through the skull and surrounding tissues must be taken into account.

It appears certain from the data available that kappa waves are not directly related to previously described bio-electrical phenomena. Of course, they closely resemble the alpha rhythm in frequency. The conditions for occurrence are, however, different - or perhaps opposite. Alpha waves generally increase in amplitude when the eyes are closed, but kappa waves show no regular differences between conditions of eyes open and eyes closed. Mental arithmetic often inhibits alpha, whereas kappa waves appear frequently during mental addition or multiplication.

The position of the electrodes suggests that the source of kappa bursts may be the temporal lobes of the brain. (Science, 12 Nov. '48 - J. L. Kennedy et al.)

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Dental Deformities and Finger-Sucking: Doctor Pearson, Associate Professor of Child Psychiatry at Temple University, states that from studies carried out by psychiatrists over a period of years, abundant evidence has accumulated to indicate that finger-sucking is a necessary part of the life of young children and that if this method of obtaining instinctual gratification is stopped too abruptly or too severely, the personality during childhood and later in adulthood becomes distorted, and the foundation is laid for neurotic illness or for antisocial behavior.

The desire for finger-sucking is a need like hunger which every child has. What the exact basis for this need is is not known, but it is known that it does exist. Because it is a need like hunger, it can be said that it has an instinctual basis, and that its gratification is necessary for the child's development. If this gratification is stopped forcibly, then the results which can occur depend on the type of child. The passive child gives in to the parent's demands, attempts to conform to please them, and remains infantile and dependent. The less passive child may attempt to conform to please the parents but develops a symptom that indicates a wish to get some pleasure from his mouth but which he is afraid to do because it has been forbidden. If the child has great courage, he resists the parent's restriction until he has to give in; then he begins to hate his parents and develop a character antagonistic to all authority. These reaction patterns once laid down continue into adult life and cause the individual and often also his environment all kinds of suffering.

Because the need to suck is an instinctual drive, its degree varies in different children. Some children relinquish finger-sucking of their own accord very early. Others continue for a moderate length of time. Others again continue to do so for a number of years and then of their own accord gradually give up first in the daytime, later after they get into bed, and still later after they fall asleep. They relinquish it entirely when they are ready emotionally to do so. Some of the cases of prolonged finger-sucking result from lack of adequate feeding in infancy and some from the lack of adequate mothering during the same period. In other cases, the need to finger-suck seems greater than usual as a constitutional trait. Difficulties in toilet training and speech defects seem to run in families, i.e., they have a constitutional basis. Similarly, constitutionally, certain families show a greater need to finger-suck. Abrupt deprivation of gratification of this need causes these children more emotional trauma than those in whom the constitutional factor is less.

There are two types of finger-sucking. In the first, the finger-sucking continues from birth for a varying period of time. In the second, the child relinquishes his finger-sucking himself and without any need to conform to the parent's dislike of it; then later, perhaps, after four or five years, the finger-sucking starts again. This type of finger-sucking has the same etiology as the similar type of enuresis and, in fact, of any neurotic symptom or of any perversion. The child has met some difficulty in his present emotional development, is unable to develop further, and goes back to an earlier form of gratification. The problem is not how to stop the finger-sucking but what has happened recently to stop his development.

It is emphasized that a general struggle between the child and a very strict and unreasonable parent causes deformity of the child's personality and that the struggle over the child's desire to gratify his need to suck is more important in causing deformity of the personality than one, for example, concerning whether the child will dress himself or not.

The question is whether finger-sucking will or will not, if undisturbed until the child is able to relinquish the gratification himself as part of his normal development, result in facial and dental deformities. Levy in his study affirmed that it does not do so unless the child sucks constantly the two middle fingers of the supinated hand, which position is very rare. It is the author's opinion that facial and dental deformities most commonly result from constitutional characteristics or conditions which impede adequate breathing, such as adenoids. (Am. J. Orthodontics, July '48 - G. H. J. Pearson)

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Prognostic Significance of Occasionally Positive Sputum After Adequate Treatment of Tuberculosis: This article concerns an attempt to find out whether patients with arrested pulmonary tuberculosis who never had any positive sputum

or gastric cultures during their last six months of hospitalization have a better prognosis than patients who meet the same diagnostic requirements, but who had one or two positive cultures during their last half year of hospitalization.

The data for this investigation are based on the records of 864 patients at the Rutland State Sanatorium, Mass. Six hundred twenty-one who had the reinfection type of pulmonary tuberculosis, were discharged with the disease arrested or apparently arrested, and were followed regularly for a period of two years or more after discharge between June 1935 and June 1945, inclusive. The records of patients who left the sanatorium in six months or less without evidence of activity of the disease during the whole period of hospitalization were excluded, as were the records of those discharged with many cultures positive for Mycobacterium tuberculosis during their last six months of hospitalization. For comparative study the records of 243 patients discharged between January 1932 and June 1935, with the disease apparently arrested, or arrested, have been used. Because previous to 1935, cultures were performed too irregularly to be of much value, the sputum specimens from this group of 243 patients were negative only on direct examination of smears and concentrates during the last six months of their sanatorium residence. Clinically and roentgenologically, the records of the members of this group are comparable to the records of those discharged from 1935 to 1945.

The exact meaning of "occasionally positive sputum" in this report is as follows. In the last six months of sanatorium residence, concentrated specimens from those patients whose sputum revealed no M. tuberculosis on stained smear were repeatedly used for culture and occasionally inoculated into guinea pigs. At least six cultures of from 24- to 72-hour specimens of sputum were made for each patient. When one or two of the cultures were positive for M. tuberculosis, the patient was considered to have "occasionally positive sputum." In this study, the cases are classified as arrested, or apparently arrested, regardless of one or two positive cultures, providing they meet with the requirements of the National Tuberculosis Association's diagnostic standard. In the records of the Rutland State Sanatorium, however, they are designated only as quiescent. The patients in whom the source of the infectious sputum could be traced definitely to endobronchial lesions through bronchoscopic examination were not discharged unless the endobronchial lesions had apparently healed.

For the purposes of study, the 621 patients were divided into two groups. Group A consisted of those with unequivocally negative sputum for the six months immediately preceding discharge; Group B of those with occasionally positive sputum. The 243 patients discharged between 1932 and 1935 with negative smears and concentrations made up Group C. Each group was subdivided according to the extent of the lesions on admission. The percentage of reactivation of the three groups of patients followed up for four years or more is shown in the table on the opposite page.

	GROUP A*	GROUP B†	GROUP C‡
	per cent	*per cent*	*per cent*
Minimal cases	11	21	21
Moderately advanced cases	20	32	38
Far advanced cases	27	52	57

* Group A represents patients with sputum negative on culture and guinea pig inoculation.

† Group B represents patients with occasionally positive sputum.

‡ Group C represents patients with sputum recorded as negative solely on the basis of examination of stained smears of individual or concentrated specimens.

The number of patients followed and the number of patients in whom reactivation of the disease occurred in the first, second, third, and fourth or more years following discharge were tabulated. The figures indicated that, in each year, the disease was reactivated more frequently in Groups B and C patients than in Group A patients. The percentage of reactivation in Group C patients in the fourth and more years after discharge was strikingly higher, but might be due to the longer period of follow-up. In the present series, none of the 108 minimal cases, in which cultures had been negative for three consecutive years after discharge of the patient, have subsequently become reactivated. The percentage of reactivation was highest in the second year for all three groups admitted to the sanatorium in all stages of the disease. It must be pointed out that most of the patients of the present study resumed full working activity in from 6 to 12 months after discharge. Whether this resumption of full working activity and the highest recurrence rate in the second year are merely incidental or related cannot be established at this time.

The Group C patients had as high a percentage of reactivation as Group B patients. If more intensive sputum studies had been made in the Group C patients (discharged between January 1932 and June 1935) with negative smears and concentrations, it would be anticipated that unequivocally negative sputum would have been found in some cases and occasionally or frequently positive sputum in other cases during the last six months of sanatorium residence. Thus, from the viewpoint of sputum findings, the prognosis of some of the patients in this group should be as good as those in Group A; in some, the prognosis should be comparable to those in Group B; and in others, it should be worse than Group B. This might explain why Group C patients had as high a reactivation rate as Group B patients, instead of a lower percentage. The data are insufficient to establish whether the more extensive use of collapse therapy in the more recently treated group of patients could account for the comparatively high percentage of reactivation of Group C. As stated above, the strikingly high percentage of reactivation of Group C patients in the fourth and subsequent years might be a reflection of the longer period of follow-up.

A comparison of Group A and Group C indicates that otherwise comparable patients, discharged with negative sputum on culture and guinea pig inoculation, fare much better than those whose sputum is recorded as negative solely on the basis of direct examination of smears of concentrates. Ordway, Medlar, and

Sasano demonstrated that cultures and guinea pig inoculation of sputum and gastric washings which were consistently negative on direct examination, yielded 35.4 percent positive results. This means that 35.4 percent of the patients discharged as apparently arrested, or arrested, according to the National Tuberculosis Association's diagnostic standard, are demonstrably infectious by culture or animal inoculation. In the present study it was found that such patients experience a reactivation of their disease twice as frequently as those whose sputum is negative on culture and guinea pig inoculation.

The future of each tuberculous patient depends on so many factors that prognostication is bound to be proved wrong in a certain percentage of cases. In this paper, many of the factors of known importance regarding the future of discharged patients were neglected because it was impossible to consider all these factors in this kind of statistical study. It appears, however, that in patients discharged with occasionally positive sputum the disease becomes reactivated more frequently than in those with unequivocally negative sputum, and that intensive sputum study in the six months immediately preceding discharge does help in the prognostication of the future of discharged tuberculous patients. (Am. Rev. Tuberc., Sept. '48 - R. Chang)

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Protective Vaccination Against Tuberculosis with Special Reference to BCG Vaccination: Accumulated experimental and clinical data indicate that an initial infection with viable virulent or attenuated Mycobacterium tuberculosis induces increased resistance to reinfection with virulent bacilli. There is, therefore, a sound basis for the use of the attenuated viable BCG strain of M. tuberculosis as an immunizing agent.

Although BCG vaccine has been used in human beings for the past 25 years, it has not received universal acceptance. The earliest objection to its use was the fear that the state of attenuation of the culture was not fixed (as Calmette claimed it was) and that it might regain its virulence. However, the innocuousness of the BCG vaccine for man is proved by the fact that, of the millions of persons who have received the vaccine, not a single unequivocal case of tuberculosis can be attributed to its use. In an animal as sensitive as the guinea pig, the author has injected routinely from 10 to 20 mg. of different lots of BCG vaccine without any evidence of progressive tuberculosis.

The most recent objection to the widespread use of BCG vaccine is based on the premise that the tuberculin reaction following the use of BCG vaccine would mask the tuberculin reaction resulting from spontaneous infection, thus making it more difficult to detect the sources of tuberculous infection. This objection might be given more serious consideration if the occurrence of tuberculosis in man more nearly approached the low rate now found among cattle in the United States. There are areas in the United States in which there is a mortality from tuberculosis of 300 and more per 100,000 population.

The evidence has not been clear cut concerning the effectiveness of the BCG vaccine in controlling tuberculosis. This, in part, is due to the difficulties inherent in any attempt to carry out a long experiment in man under controlled conditions. Moreover, an evaluation of the effectiveness of BCG vaccine on the basis of a reduction of the disease as compared with previous years is not valid since for many years there has been a steady decline of tuberculosis.

Although there has been a widespread use of BCG vaccine in man in some of the countries of Continental Europe, the Scandinavian countries, the countries of South America, and in Japan, these programs were not carried out under the controlled conditions necessary for determining conclusiveness of the evidence. Nevertheless, there is a considerable amount of circumstantial evidence that the use of the vaccine has reduced the morbidity and mortality from tuberculosis.

The value of BCG vaccine in increasing resistance to tuberculous reinfection among some Indians of the United States and Alaska was investigated by the author under carefully controlled conditions. Freshly prepared BCG vaccine was administered intracutaneously to 1,551 American Indians ranging in age from less than one year to 20 years and to 123 newborn infants. At the same time 1,457 Indians of comparable age and living under the same conditions received an intracutaneous injection of sterile physiological saline and served as controls. One hundred and thirty-nine newborn infants also served as controls.

No untoward local or general reaction followed the injection of the vaccine, nor did the regional lymph nodes ulcerate in any instance.

The original groups of those vaccinated and controls were followed over a period of from 9 to 11 years by means of tuberculin tests and roentgenograms of the chest, and the group of "newborn" infants was similarly followed for from 6 to 8 years. This amounted to observation for a total of 16,406 person-years for those vaccinated and 15,207 person-years for the controls. The mortality rate from all causes was 3.1 per 1,000 person-years of observation for the vaccinated and 7.2 for the controls. In other words, among the 1,551 BCG-vaccinated persons there occurred a total of 55 deaths, including 6 deaths from tuberculosis, and among the 1,457 controls there occurred a total of 109 deaths, including 53 deaths from tuberculosis. Thus, the mortality rate from tuberculosis per 1,000 person-years of observation was 0.4 for those vaccinated and 3.5 for the controls.

Among the controls the death rate from tuberculosis was highest among the males in the age groups from 15 to 19 years and from 20 to 24 years; and in the females in the age groups from 10 to 14 years and from 15 to 19 years. It was approximately twice as high among the females as among the males.

Among the 123 newborn infants, who were vaccinated and observed for from 6 to 8 years, 7 have died, none from tuberculosis. Among the 139 newborn controls, 15 have died, 4 of them from tuberculosis.

The tuberculin reaction became positive one year after vaccination in 93.3 percent of those vaccinated and has remained at approximately the same level throughout the course of this study. Among the controls the tuberculin reaction became positive in 12.7 percent within one year after the initial negative reaction, and there has been a constant and gradual increase in the percentage of the controls reacting to tuberculin.

Roentgenologically demonstrable lesions having the characteristics of primary tuberculosis occurred in 22 of the vaccinated and in 120 of the controls. Minimal lesions of reinfection type, progressive lesions, and miliary and extrapulmonary lesions of tuberculosis were found in 21 of the vaccinated and in 93 of the controls.

Concerning the advisability of the universal use of BCG vaccine, there is room for a difference of opinion. Certainly in those areas where the morbidity and mortality from tuberculosis are high, living conditions poor, and hospital facilities for the care of patients with manifest cases of tuberculosis inadequate, the use of BCG vaccination is indicated. Moreover, its use is definitely indicated in medical students, nurses, and other medical personnel who are tuberculin negative and who may be exposed frequently to tuberculous infection. For military personnel who are tuberculin negative and who are on duty in areas with a high incidence of tuberculosis, BCG vaccination should be carried out. Conversely, in areas where the morbidity and mortality from tuberculosis are low and falling, where homes are widely scattered, and housing and hospital facilities adequate, the universal use of BCG vaccine is debatable.

One of the immediate needs in the field of BCG vaccination is the establishment of uniform procedures for the administration and standardization of the vaccine. The question of setting up standards for potency and optimum dose remains to be solved, and methods of maintaining the viability of the bacterial suspension for a long period of time must be developed. (Am. Rev. Tuberc., Sept. '48 - J. D. Aronson)

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Thermal Insulation and Comfort Characteristics of Fibrous-Glass-Lined Garments: In this study, little confirmation could be found for claims sometimes made that fibrous glass-lined garments offer much warmth with a minimum of weight. In testing a fibrous-glass-lined jacket comparatively with two wool-pile jackets, its performance on a thickness basis was the poorest of the three, even though it showed a higher insulation value per pound of weight. The mean insulation value was about 37 percent lower than that of the wool-pile garments. Moreover, the body skin temperatures of the subjects wearing it dropped faster, and they shivered sooner on exposure to a temperature of 0° F. than they did when wearing wool-pile garments. Subjectively, too, the fibrous-glass-lined jacket was the coldest of the three.

The chief objection to fibrous-glass insulation, as now used in cold-weather clothing, is its poor resistance to compression. Pressures which normally occurred in the back and elbow of subjects sitting on an arm chair reduced the insulation of glass lining to about one fourth of the maximum value observed in parts of the jacket not subjected to compression. Under similar conditions, loss of wool pile insulation was only half as much. Even slight pressures of less than 0.05 lb. per sq. in. seem to affect fibrous-glass insulation.

An advantage of fibrous-glass is its relatively low absorption of body moisture, which under the test conditions was less than half of that of wool. The property of low water absorption might prove significant in physical exercise, but proof has yet to come. (J. Indust. Hyg. and Toxicol., Sept. '48 - C. P. Yaglou, through Indust. Hyg. Digest, Oct. '48)

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New X-Ray Absorbing Glass: A new glass, containing over 20 percent of tungsten oxide and about 60 percent of lead oxide, has been developed for the protection of scientists from harmful rays during research. Features outstanding in this new development include a high absorption efficiency. The refraction index of 1.993 compares with 1.6 in the average glass. It is claimed that the new glass will not discolor or turn brown or black when exposed to the x-ray or gamma ray. Thus it will give better visibility in the scientists' work. (National Glass Budget, 16 Oct. '48, through Industrial Hyg. Digest, Oct. '48)

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Caution Concerning Homologous Serum Jaundice: Homologous serum jaundice may be transmitted to individuals through the use of unsterile syringes, needles, and other equipment to administer parenteral injections or to collect blood specimens. Although the virus of this disease is relatively resistant to many of the usual bactericidal agents, heat apparently will destroy it.

All instruments, including syringes, needles, lancets, and rubber tubing used for injections or for the collection of blood specimens must be sterile. Sterilization by dry heat or autoclaving is preferable and is strongly recommended. However, when this is impracticable, instruments may be sterilized by boiling for a minimum of five minutes.

In the elimination of the hazard of transmitting infections, the following should be routinely observed:

a. Skin puncture to obtain blood for blood counts, hemoglobin determinations, etc. (1) Because hollow needles and "automatic" or spring lancets cannot easily be cleaned and sterilized, they should never be used. (2) Plain lancets, solid needles, or knife blades used for skin puncture should be carefully sterilized by heat. No needles, lancets, or knife blades should be re-used until after complete sterilization by heat.

b. Venipunctures for collecting blood specimens. (1) Only sterile syringes and needles should be used because, otherwise, small amounts of infectious material may find their way into the vein by reflux when the tourniquet is removed prior to withdrawal of the needle. (2) Bleeding with the sterile needle only is considered to be the most practicable technic when large numbers of specimens are to be taken, as for serologic tests. (3) Accidental contamination of needle shafts should be avoided.

c. Parenteral injections. (1) For each person receiving intravenous or intramuscular injections, an individual, heat-sterilized syringe must be used and no syringe or needle should be used again until it has been resterilized. (2) In immunizing groups of people, it is imperative that a heat-sterilized syringe and needle be used for each person except in the most unusual circumstances, such as in mass immunization, in which it may be necessary for certain reasons to use a syringe containing more than one dose. In such cases, a syringe containing not more than ten doses of the immunizing agent should be used. However, a fresh, heat-sterilized needle must be used for each person. When emptied, the syringe must be resterilized by heat before re-use. If, at any time, blood or tissue fluid is aspirated into the syringe, including its hub, the contents of the syringe should be discarded, and the syringe sterilized before re-use.

All personnel of the Medical Department should familiarize themselves with this article and take the necessary steps to prevent the spread of infection by the use of improperly sterilized equipment. (Professional Div., BuMed)

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Applications Regarding Eligibility to Take Examination for Certification by Various Specialty Boards: In accordance with Circular Letter No. 47-163, all medical officers who consider themselves eligible to apply for permission to take the examination for certification by a particular American Specialty Board are required to apply directly to the Bureau of Medicine and Surgery for an evaluation of their training credits. This procedure is now identical with that followed by candidates who seek admission to either the American College of Surgeons or the American College of Physicians and represents a change, in that previously requests for admission to examination by a specialty board were to be forwarded by the applicant directly to the secretary of the cognizant board. Medical officers should withhold correspondence with secretaries of specialty boards until advised to do so by BuMed.

Circular Letter No. 47-163 states that although the method for keeping a log of professional assignment is obsolete, medical officers who have been keeping such logs should not destroy them because they may be useful in compiling data for the secretary of a specialty board. Residents in naval and civilian hospitals should keep an accurate record of all work performed including lectures, seminars, and grand rounds. These records should be signed by the head of the service at the completion of each training period.

Circular Letter No. 47-163 canceled the article, "Applications for Eligibility for Examination for Certification by Various Specialty Boards," in the News Letter dated 17 January 1947, Volume 9, No. 2, page 23. (Professional Div., BuMed)

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Voluntary Retirement: See page 36 for a copy of BuPers Circular Letter No. 48-202 of 20 October 1948 which appears in the 31 October issue of the Navy Department Bulletin.

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BUMED CIRCULAR LETTER 48-123 12 November 1948

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-6, MMD.

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change 3-6 is effective immediately. It shall be recorded on the "Record of Changes" page in the Manual. The individual paragraph changes are to be inserted in their proper places in the Manual text. At a later date, these changes will be incorporated in printed page change 3.

--BuMed. H. L. Pugh

Note: The enclosure consists of 14 pages of miscellaneous changes in the MMD. -Ed.

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BUMED CIRCULAR LETTER 48-124 15 November 1948

To: Distribution List

Subj: Naval Medical Supply Depot, Guam, M.I.: Mission of

Ref: (a) CNO ltr Op-40U-1er, L8-2, Serial 798P40, dtd 25 Oct 1948.
(b) BuMed Circular Letter No. 48-33 dtd 19 Mar 1948.

1. In accordance with the authority contained in reference (a), paragraph 1(c) is changed to read:

"To provide medical supply support to Naval forces afloat at or calling at Guam."

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-125 17 November 1948

To: MedOfCom, NavMedCens, and NavHosps

Subj: Naming of Roads, Streets, Circles, etc.: BuMed Policy with Reference to

This letter (1) states that the naming or renaming of roads, streets, lanes, circles, athletic fields, and similar installations within the limits of naval medical centers and naval hospitals shall be effected only upon written approval of BuMed (for purposes of uniformity in naming methods), (2) sets forth the criteria by which names are to be selected, and (3) requests that addressees at activities having streets and other installations presently unnamed or inappropriately named submit to the Bureau suggestions for naming or renaming these installations.

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BUMED CIRCULAR LETTER 48-126 17 November 1948

To: BuMed Management Control Activities

Subj: Physical Inventory of Facilities Located at BuMed Management Control Activities; Completion of.

Refs: (a) SecNav ltr M625/E.R.C:NKC, Serial 138, dtd 10 May 1946.
(b) BuMed Circular Letter 46-166.

This letter directs that addressees take the necessary steps to insure that by 1 January 1949 (1) the inventories prescribed by references (a) and (b) have been completed and (2) copies of the covering property record cards have been forwarded to BuSandA as required by paragraph 63017 of BuSandA manual.

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BUMED CIRCULAR LETTER 48-127 17 November 1948

To: MedOfsCom, NavHosps

Subj: Letters Written to Next of Kin in Cases of Death Occurring in Naval Hospitals

Refs: (a) Paragraph D-9601(2), BuPers Manual
(b) Paragraph 3417.2, MMD

It is requested in this letter that addressees forward to BuMed, marked for attention of Code 214, two examples of letters currently being forwarded to the next of kin of deceased naval personnel in compliance with instructions in references (a) and (b).

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BUPERS CIRCULAR LETTER 48-202 20 October 1948

To: All Ships and Stations

Subj: Voluntary Retirement

Ref: (a) BuPers Circ. Ltr. 178-47; AS&SL July-Dec. 1947, 47-864, p. 327

1. It has come to the attention of the Chief of Naval Personnel that officers who submit requests for voluntary retirement may prematurely enter into extensive civilian commitments prior to the final approval of such requests.

2. It is desired to point out to all officers that voluntary retirement with less than 40 years of service is a privilege and not an unrestricted right. Reference (a) specifically states that requests for voluntary retirement from officers with less than 40 years of service are accepted "in the discretion of the President." This letter is not a change in policy and will not operate to eliminate acceptance of voluntary retirements prior to acquisition of 40 years service, but it does accentuate the fact that each case will be judged on its merits considering the needs of the naval service and the circumstances of the individual.

3. Accordingly, officers who may contemplate requesting voluntary retirement should not expose themselves to embarrassment by assuming specific civilian commitments prior to the final approval of such requests.

--BuPers. T. L. Sprague

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